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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,949	DAVIS ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/261,448 with a priority date of January 12, 2001.

Claims 1-24 are currently pending.

Election/Restrictions

1. Applicant is reminded that claims 1-24 are the subject of examination in the present Office Action ONLY TO THE EXTENT that they read upon MHC class I complexes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 7 and 8 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It was previously stated: "Claims 7 and 8 recite the limitation "F," "S" and "P" in the body of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 7 and 8 earlier recite only the formulas $(F_1S_1)_n$ in claim 7 and $(F_1S_1P_1)_n$ in claim 8. There is no basis for reciting F, S, or P and the terms F_1, S_1, and P_1 are left undefined in the claims."

Applicant's arguments filed April 3, 2006 have been fully considered but they are not persuasive.

Applicant argues that the terminology used is standard chemical terminology denoting how many times a particular element occurs in a chemical formula and that the terms therefore do not require antecedent basis. However, there is no provision in the claims for any of the elements within the formula to occur a variable number of times. As set forth in the claims, each element F, S or P occurs only a single time. To separately denote each of the terms with a subscript that is not defined in the claim implies that each or all of the elements may occur more than once, but such an interpretation is not supported in the claim. Applicant must either remove the subscripts from the formulae recited in claims 7 and 8 or include the subscripts in the definitions of elements F, S and P.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-17 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene [1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002).

It was previously stated: "Altman teaches a recombinant fusion protein comprising an MHC class I heavy chain and a multimerization domain consisting of a 15 amino acid substrate for BirA-dependent biotinylation (page 94, third column in particular)[claim 1]. Altman teaches creation of a nucleic acid molecule expressing the fusion protein, a vector comprising the nucleic acid and a host cell expressing the fusion protein (page 96, second column in particular)[claims 2-5]. Claim 24 is included because the 15 amino acid substrate for BirA-dependent biotinylation incorporates a flexible peptide spacer separating the biotinylation site from the MHC molecule.

Altman does not teach the incorporation of a GFP-like chromophore into the fusion protein.

Cormack teaches FACS-optimized mutants of the GFP protein that can be incorporated into expressed proteins comprising a 20 amino acid region surrounding the chromophore (amino acids 55-74 of GFP, comprising the chromophore site of amino acids 65-67) (Abstract and page 34 in particular). Cormack teaches that these GFP-like mutants are superior because they may be detectable in systems in which wild-type GFP fluorescence is not visible.

Altman teaches the association of the fusion proteins with beta-2-microglobulin and the multimerization of the MHC complexes by incubation with deglycosylated avidin (paragraph bridging pages 33-34 in particular) and incorporation with a peptide antigen (paragraph bridging columns 1-2 of page 95 in particular)[claims 6-10].

Altman teaches a method of detecting, enumerating and enriching T cells reactive with the multimeric complexes (Figs. 1-2 in particular) [claims 11-13, 16, 17].

Altman further teaches a method comprising additional staining of the T cells with fluorescently labeled antibodies for pan-T cell (CD62L) and activation (CD38) markers (Figure 3 in particular) [claims 14, 15].

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to incorporate the GFP-like mutants of Cormack into the fusion protein of Altman between the MHC class I alpha extracellular domain and the multimerization domain in order to make an intrinsically fluorescent fusion protein. One would have been motivated, with a reasonable expectation of

success to combine the teachings because the mutants taught by Cormack comprise the fluorescent domain internal to the small 20 amino acid segment and it therefore would retain the ability to fold properly to fluoresce. The artisan would further be motivated to combine the references with a reasonable expectation of success by the knowledge that the construct will have a 1:1 ratio between the level of fluorescence and the number of MHC class I molecules detected in an assay. The artisan would find this valuable for retaining correlation not only between samples within an assay, but also between assays because the level of fluorescence can vary between preparations of phycoerythrin labeled avidin molecules."

Applicant argues that the claims are not obvious because Altman's teaching of a BirA substrate does not constitute a multimerization domain, as the BirA substrate require biotinylation for multimerization via binding of the biotin moieties to streptavidin. Applicant argues that Altman does not teach or suggest self-multimerization by the GFP-like domains as embraced by the instant invention. However, Applicant is arguing elements from the specification that are not part of the claims. While the claims are to be read in light of the specification, limitations from the specification are not to be read into the claims. There is no requirement in the claims for any of the domains of the polypeptide construct to be self-multimerizing, only that the construct contain a multimerization domain. Furthermore, the claims are to be given their broadest reasonable interpretation. As such, a multimerization domain can reasonably be understood to mean a domain that allows for the multimerization of the construct. The BirA allows the construct to be biotinylated through the action of BirA. The biotin is then bound to avidin or streptavidin in order to create a multimeric complex comprising multiple MHC molecules. Accordingly, as the BirA substrate facilitates, and is included in the recombinant molecule for the purpose of, the multimerization of the construct, the BirA substrate domain fully satisfies the metes and bounds of the term "multimerization domain." Applicant further argues that Cormack does not supply the missing element because Cormack is silent about the ability of some GFP-like chromophores to self-multimerize. However, again Applicant is arguing an element that is not part of the claims. The claims require that the recombinant fusion protein comprises "a GFP-like chromophore" and "at least one multimerization domain." There is no requirement in the claims that the chromophore and the multimerization domain be one-in-the-same element of the fusion construct. Accordingly, provision of a multimerization domain according to the teachings of Altman along with the provision of a separate GFP-like chromophore according to the teachings of Cormack fully satisfies the metes and bounds of the claimed invention.

4. Claims 18-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene

[1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002) as applied to claims 1, 7 and 8 above, and further in view of U.S. Patent No. 6,232,445 to Rhode et al (A on form PTO-892).

It was previously stated: "Altman and Cormack have been discussed supra.

The combined references do not specifically teach gathering the components together in a kit form.

The '445 patent teaches that recombinant MHC molecules can be incorporated "as one component of a kit suitable for medical, research, home or commercial use" (column 10, lines 16-29 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to prepare the reagents prior to performing an assay and storing them as separate compositions in a kit form. The artisan would have been motivated to create such a kit with a reasonable expectation of success by the knowledge that such a prepackaged kit would expedite the handling of samples when received from a clinical setting."

Applicant has not provided substantive argument regarding the teachings of the '445 patent, relying instead upon the alleged deficiencies of the teachings of Altman in view of Cormack, which have been addressed supra. Accordingly, the instant ground of rejection stands without any further explanation.

5. Claim 23 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene [1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002) and U.S. Patent No. 6,232,445 to Rhode et al (A on form PTO-892) as applied to claims 18 and 21 above, and further in view of U.S. Patent No. 4,902,613 to Chang et al (B on form PTO-892).

It was previously stated: "Altman, Cormack and the '445 patent have been discussed supra.

The combined references do not teach the inclusion of a red blood cell lysing agent in a kit.

The '613 patent teaches that approximately 90% of the cells in peripheral blood are red blood cells while lymphocytes make up the minor percentage of about 10% (column 1 in particular). The '613 patent teaches that this lysis of the red blood cells allows clean identification of different types of lymphocytes by means of flow cytometry (column 3, lines 36-64 in particular). the '613 patent teaches an agent that selectively lyses the red blood cells, leaving the lymphocytes intact (column 3, line 65 through column 4, line 62 in particular).

Altman teaches the analysis of cell staining by means of flow cytometry, but is silent about the use of a red blood cell lysing agent. Cormack teaches that the GFP-like mutants are optimized for use in flow cytometry.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to include the red blood cell lysing agent of the '613 patent in a kit for the analysis of MHC multimer binding to target T cells. the artisan would have been motivated to ad the reagent to a kit with a reasonable expectation of success by the knowledge that the assay is searching for a subset of cells which comprise only a small portion of the minor population of cells obtainable from a peripheral blood sample. Accordingly, elimination of 90% of the cells from the sample, cells that are irrelevant to the assay anyway, would increase the sensitivity of the assay for the target cells.

Applicant has not provided substantive argument regarding the teachings of the '445 and '613 patents, relying instead upon the alleged deficiencies of the teachings of Altman in view of Cormack, which have been addressed supra. Accordingly, the instant ground of rejection stands without any further explanation.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
November 25, 2005

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